REMARKS

Claims 100, 106, 107, 109, 110 and 112-125 are pending in the subject application. Applicants hereinabove have amended the specification, and amended claims 100, 109, 110, 112, 114, 115, 118, 124 and 125. Accordingly, upon entry of this Amendment, claims 100, 106, 107, 109, 110 and 112-125, as amended, will still be pending and under examination.

Applicants have amended claim 118 to correct a minor typographical error. Applicants maintain that the amendments to the specification and to claims 100, 109, 110, 112, 114, 115, 118, 124 and 125 do not raise any issue of new matter, and that these claims, as amended, are fully supported by the specification as originally filed.

Support for the claim amendments is found, *inter alia*, in the specification as follows: **Claims 100, 112, 114 and 115**: page 11, line 33 to page 12, line 29, page 12, lines 15-16, page 14, lines 1-5, page 32, lines 13-20, and Figures 1-1 and 1-2; **Claim 109**: page 87, lines 27-29, and page 37, lines 31-35; **Claims 110, 124 and 125**: page 12, lines 15 and 16, page 16, lines 26-28, and page 66, lines 8-14.

In view of the comments set forth below, applicants maintain that the grounds of the Examiner's rejections made in the April 16, 2004 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw these grounds of rejection.

February 3, 2004 Examiner's Proposed Amendment and February 6, 2004 Examiner's Interview

On February 3, 2004, the Examiner forwarded to the undersigned's office a proposed Examiner's Amendment for the subject application and for related copending applications (U.S. Serial Nos. 08/196,154 and 08/481,809) which applicants understood would place this application in condition for allowance. Applicants note for the record their appreciation for the courtesies extended by Examiner Holleran to their representatives, John P. White, Esq., and Mark A. Farley, Esq. in providing the proposed Examiner's Amendment. For completeness of the record, applicants submit herewith as **EXHIBITS A** and **B** copies of the February 3, 2004 Examiner's Proposed Amendments in connection with related U.S. Serial Nos. 08/196,154 and 08/481,809, respectively.

On February 6, 2004, applicants' undersigned attorney, Mark A. Farley, Esq., had a telephonic interview with Examiner Holleran concerning the February 3, 2004 Examiner's Proposed Amendment in connection with this application and related copending applications (U.S. Serial Nos. 08/196,154 and 08/481,809). Applicants again wish to thank the Examiner for her time and consideration during this interview. For completeness of the record, applicants submit herewith as **EXHIBITS C** and **D** copies of the February 3, 2004 Examiner's Proposed Amendments in connection with related U.S. Serial Nos. 08/196,154 and 08/481,809, respectively.

Subsequently, on April 16, 2004, Examiner Holleran issued the Office Action to which this Amendment is a response.

Thereafter, on August 12, 2004, the undersigned had a telephonic interview with Examiner Holleran concerning the February 3, 2004 Examiner's Proposed Amendment in the related U.S. application (U.S. Serial No. 08/196,154), which is similar to the February 3, 2004 Examiner's Proposed Amendment in the subject application. For completeness of the record, applicants submit herewith as **EXHIBIT E** a copy of the Interview Summary for that interview.

Applicants have carefully reviewed the February 3, 2004 proposed Examiner's Amendment and have substantially incorporated it into this Amendment. However, applicants have made certain changes which are believed necessary, for example, to correct minor typographical errors and to insure proper antecedent basis in the amended claims. Applicants maintain that this Amendment places this application in condition for allowance and look forward to receiving from the Examiner a communication to this effect.

Rejections Withdrawn In The April 16, 2004 Office Action

The Examiner stated that the objection to the disclosure is withdrawn in view of the submission of a new "Figure 6B."

The Examiner stated that the provisional rejection of claims 100-126 under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claims 123-146 of copending Serial No. 08/477,147 is withdrawn in view of the terminal disclaimer filed December 15, 2003.

The Examiner also stated that the provisional rejection of claims 100-126 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 119-143 of copending Serial No. 08/196,154 is withdrawn in view of the terminal disclaimer filed December 15, 2003.

The Examiner also stated that the objection to claim 95 for depending from a cancelled claim (claim 94) is withdrawn in view of the cancellation of claim 95.

The Examiner also stated that the rejection of claims 103-105 and 126 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, is withdrawn in view of the cancellation of the claims.

The Examiner also stated that the rejection of claims 100-112 under 35 U.S.C. §103(a) as being unpatentable over Wiegand et al. (U.S. Patent 5,599,914, issued February 4, 1997) in view of Fiume et al. (Critical Rev. Therapeutic Drug Carrier Systems, 4(4):265-284 (1988)), Ritter et al. (Seminars in Cancer Biology, 2:401-409 (1991)), Kensil et al. (The Journal of Immunology, 146(2):431-437 (1991), Marciani et al. (Vaccine, 9:89-96 (1991)) and Uemura et al. (J. Biochem., 79(6):1253-1261 (1976)) is withdrawn.

The Examiner also stated that the rejection of claims 100, 112-115 and 117-126 under 35 U.S.C. §103(a) as being unpatentable over Wiegand et al. (U.S. Patent 5,599,914, issued February 4, 1997), Fiume et al. (Critical Rev. Therapeutic Drug Carrier Systems, 4(4):265-284 (1988)), Livingston et al. (Cancer Research, 149:7045-7050 (1989)), in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409 (1991)), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al. (The Journal of Immunology, 146(2):431-437 (1991), Marciani et al. (Vaccine, 9:89-96 (1991)) and Uemura et al. (J. Biochem., 79(6):1253-1261 (1976)) is withdrawn.

The Examiner further stated that the rejection of claims 95, 115 and 116 under 35 U.S.C. §103(a) as being unpatentable over Wiegand et al. (U.S. Patent 5,599,914, issued February 4, 1997) in view of Fiume et al. (Critical Rev. Therapeutic Drug Carrier Systems, 4(4):265-284 (1988)), Livingston et al. (Cancer Research, 149:7045-7050 (1989)), Ritter et al. (Seminars in Cancer Biology, 2:401-409 (1991)), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al. (The Journal of Immunology, 146(2):431-437 (1991), Marciani et al. (Vaccine, 9:89-96 (1991)) and Uemura et al. (J. Biochem., 79(6):1253-1261 (1976)) as applied to claims 78, 80-92, 94 and 96-99 above and further in view of Irie et al. (U.S. Patent No. 4,557,931) is withdrawn.

Formalities

The Examiner objected to claims 109 and 112 under 37 C.F.R. §1.75(b) because claims 109 and 112 appear to

claim inventions of the same scope.

In response, applicants point out that claim 109, as amended above, now recites "50 μg." Thus, applicants maintain that the Examiner's objection to claims 109 and 112 has been obviated.

Terminal Disclaimer filed December 15, 2003

As mentioned above, applicants filed a Terminal Disclaimer on December 10, 2003 (which the U.S. Patent and Trademark Office received on December 15, 2003) relative to any patent issuing from copending U.S. Serial Nos. 08/196,154 and 08/477,147 in response to then outstanding provisional obviousness-type double patenting rejections of claims 100-126.

Applicants intend to submit a substitute Terminal Disclaimer with respect to any patent issuing from any one or more of copending U.S. Serial Nos. 08/196,154, 08/475,784, 08/477,147, and/or 08/481,809 in the near future. Applicants note that the substitute Terminal Disclaimer will replace and supersede in all respects the Terminal Disclaimer filed December 15, 2003.

Claim Rejection Under 35 U.S.C. §112, First Paragraph - Written Description

The Examiner rejected claims 100, 106, 107, 109, 110 and 112-125 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner stated that the specification does not support the genus of conjugates comprising gangliosides, wherein the ganglioside has "an altered ceramide portion comprising an altered sphingosine base."

The Examiner stated that the claimed inventions read on compositions comprising ganglioside conjugates and methods of treatment comprising the administration of compositions comprising ganglioside conjugates, where the ganglioside portions of the conjugates are so broadly claimed that they are not adequately described by the specification. Specifically, the Examiner stated that the recitation "GM2 or GD2 ganglioside derivative" which comprises "an altered ceramide portion comprising an altered sphingosine base" refers to a genus of compounds that is not supported by the specification. The Examiner stated that the only example of an "altered ceramide portion comprising an altered sphingosine base" provided by the specification is the one example of a ganglioside conjugate in which, prior to conjugation, the sphingosine base has been cleaved with ozone and reduced to form a reactive aldehyde at the C-4 carbon of the sphingosine base. The Examiner also stated that this one example is not representative of all the possible species encompassed by the phrase "GM2 or GD2 ganglioside derivative" which comprises "an unaltered oligosaccharide part and an altered ceramide portion comprising an altered sphingosine base." The Examiner thus concluded that the genus of conjugates is not supported by an adequate written description of the varied members of the

genus, and one of skill in the art would not find that applicants were in possession of the genus of claimed compositions or claimed methods using the claimed compositions at the time of filing.

In response to the Examiner's rejection to claims 100, 106, 107, 109, 110 and 112-125, but without conceding the correctness thereof, applicants note that claims 100, 109, 110, 112, 114, 115, 118, 124 and 125 have been amended. These claims, as amended, do not recite the phrase "an altered ceramide portion comprising an altered sphingosine base." Instead, they only refer to an altered sphingosine base, the nature of the alteration being further defined elsewhere in the claim.

In view of the amendments to the claims, applicants maintain that claims 100, 106, 107, 109, 110 and 112-125 satisfy the requirements of 35 U.S.C. §112, first paragraph, and request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner also rejected claims 100, 106, 107, 109, 110 and 112-125 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner stated that the specification does not support the genus of conjugates comprising "a derivative of Keyhole Limpet Hemocyanin."

The Examiner stated that the specification fails to provide a definition of what is encompassed by the phrase "derivative of Keyhole Limpet Hemocyanin (KLH)," but instead provides examples of derivatives where compounds such as cytokines, non-ionic block copolymer or monphospholipid A are linked to KLH. The Examiner also stated that these examples of derivatives are not representative of the full scope of the genus of "derivatives" of KLH because, absent a definition in the specification limiting the derivatives to those species described, a "derivative" is interpreted to mean any compound that comprises any portion of KLH, even a portion as small as one molecule of KLH. The Examiner thus concluded that the scope of "derivative" of KLH is not supported by the few examples provided by the specification. The Examiner further concluded that the genus of conjugates is not supported by an adequate written description of the varied members of the genus, and one of skill in the art would not find that applicants were in possession of the genus of claimed compositions or claimed methods using the claimed compositions at the time of filing.

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants note that claims 100, 109, 110, 112, 114, 115, 124 and 125 have been amended. These claims, as amended, do not recite the phrase "a derivative of Keyhole Limpet Hemocyanin." Rather, they only refer to "Keyhole Limpet Hemocyanin."

In view of the amendments to the claims, applicants maintain that claims 100, 106, 107, 109, 110 and 112-125

satisfy the requirements of 35 U.S.C. §112, first paragraph, and request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejection Under 35 U.S.C. §112, Second Paragraph - Indefiniteness

The Examiner rejected claims 100, 106, 107, 109, 110 and 112-125 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that claims 119, 129, 131 and 132 are indefinite because of the recitation of "QS-21". The Examiner stated that the specification does not describe with sufficient clarity the chemical and structural nature of "QS-21." The Examiner stated that the specification appears to define QS-21 is as an example of one of the saponins and to reference literature that teaches one how to isolate QS-21 from a mixture of saponins. The Examiner also stated that because QS-21 appears to be an essential ingredient of the claimed invention, the attempt to describe QS-21 and how it is isolated is an attempt at incorporation by reference of matter essential to the practice of the claimed invention. The Examiner further stated that the references cited are not available for incorporation by reference because they are non-patent publications.

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants, as proposed by the Examiner in the February 3, 2004 Examiner's Proposed Amendment, have hereinabove amended

the specification to incorporate explicitly subject matter previously incorporated by reference from Kensil, et al. "Separation and Characterization of Saponins with Adjuvant Activity from *Quillaja saponaria* Molina Cortex", Journal of Immunology, 146(2):431-437 (January 15, 1991) and Newman, et al., "Saponin Adjuvant Induction of Ovalbumin-Specific $CD8^+$ Cytotoxic T Lymphocyte Responses", Journal of Immunology, 148(8):2357-2362 (April 15, 1992). Kensil, et al. and Newman, et al. are expressly incorporated on page 66, line 10 and page 128, line 27 to page 129, line 2 of the specification, and are designated as reference numbers "10" and "11", respectively, in the Third Series of Experiments.

Specifically, applicants have amended the specification to incorporate the first two paragraphs of the "Materials And Methods" section on page 432 of Kensil, et al. and footnote 2 on page 2357 of Newman, et al.

In accordance with M.P.E.P. §608.01(p)(I)(A)(2), applicants' undersigned attorney states that the amendatory material from Kensil, et al. and Newman, et al. consists of the same material incorporated by reference in the referencing application, and that the specification, as amended, does not raise any issue of new matter.

In view of the above remarks, applicants maintain that amended claims 100, 106, 107, 109, 110 and 112-125 satisfy the requirements of 35 U.S.C. §112, second paragraph, and request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner also rejected claims 100, 109, 110, 112, 114, 115, 124 and 125 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that claim 111 is indefinite because the phrase "the saponin" lacks antecedent basis.

In response to the Examiner's rejection, applicants note that claims 100, 109, 110, 112, 114, 115, 124 and 125 have been amended. Claims 100, 109, 110, 112, 114, 115, 124 and 125, as amended, does not recited the phrase "the saponin." Rather, they only refer to "QS-21."

In view of the amendments to the claims, applicants maintain that claims 100, 109, 110, 112, 114, 115, 124 and 125 satisfy the requirements of 35 U.S.C. §112, second paragraph, and request that the Examiner reconsider and withdraw this ground of rejection.

Rejections Under 35 U.S.C. §103(a) - Obviousness

The Examiner rejected claims 100, 114, 115 and 117-125 under 35 U.S.C. §103(a) as allegedly unpatentable over Wiegand (U.S. Patent No. 5,599,914, issued February 4, 1997) in view of Jennings (U.S. Patent No. 4,356,170, issued October 26, 1982), in view of Neurath (U.S. Patent No. 4,591,552, issued May 27, 1986), in view of Ratcliff (U.S. Patent No. 5,344,870, issued September 6, 1994), in view of Patrick (U.S. Patent No. 4,652,629, issued March

24, 1987), in view of Blincko (U.S. Patent No. 5,256,409, issued October 26, 1993), in view of Marciani (Vaccine, 9:89-96 (February 1991)), in view of Ritter (Seminars in Cancer Biology, 2:401-409 (1991)), in view of Tsuchida (Journal of the National Cancer Institute, 78:45-54 (1987)), and further in view of Livingston (Proc. Natl. Acad. Sci. USA, 84:2911-2915 (May 1987)).

The Examiner stated that Wiegand discloses glycoconjugates comprising gangliosides conjugated to carrier proteins, wherein the ganglioside has been ozonolyzed and reduced at the C-4 double bond of the sphingosine base to produce a reactive aldehyde intermediate that may be reacted directly with free amines present in carrier proteins to form a conjugate (citing to col. 1, line 11 to col. 2, line 44), wherein the ganglioside may be GM3, GD3, GM2 or GM1. The Examiner stated that Wiegand teaches that the coupling of gangliosides to carrier proteins is appropriate of all gangliosides, and that glycoconjugates of gangliosides are useful as vaccines (citing col. 1, lines 50-55). The Examiner acknowledged that Wiegand fails to explicitly teach that the bond between the aldehyde group of ozonolyzed and reduced ganglioside and the carrier protein would be via a lysine residue of the carrier protein. The Examiner also acknowledged that Wiegand fails to specifically teach a glycoconjugate comprising the specific carrier protein, KLH, and fails to teach a glycoconjugate having a ganglioside to KLH molar ratio of about 200:1 to 1400:1. The Examiner also acknowledged that Wiegand fails to teach a glycoconjugate within a composition containing a saponin. The Examiner also

acknowledged that Wiegand fails to teach the specific range of amounts of conjugated ganglioside in a composition, where the amounts are about 1μg to about 200μg.

The Examiner stated that Jennings discloses the chemistry of linking a carbohydrate containing a reactive aldehyde group to a carrier protein is well known and likely would be via a lysine (citing col. 3, lines 40-46 and claims 11 and 18 at cols. 9 and 10, respectively).

The Examiner stated that Ratcliff, Patrick and Blincko disclose that KLH was known as a useful carrier protein for carbohydrate antigens (citing Ratcliff, col. 29, lines 46-51), small peptide antigens (citing Patrick, col. 9, lines 7-28), and for tricyclic antidepressant drugs (citing Blincko, col. 7, lines 29-41).

The Examiner stated that Ritter discloses the desirability of conjugating gangliosides to KLH. The Examiner stated that Ritter discloses that covalent attachment to KLH results in the production of IgG antibodies in melanoma patients, and that the production of IgG antibodies is desirable because IgG antibodies are of higher affinity, better able to penetrate solid tissue, able to mediate antibody-dependent cell-mediated cytotoxicity and remains in the circulation for longer periods after immunization (citing page 106, 1st col.).

The Examiner stated that Neurath, using KLH as the carrier protein and the SPDP heterobifunctional linker method of Wiegand, teaches peptide-KLH conjugates contain

approximately 200 peptide molecules per KLH (citing col. 17, lines 15-40).

The Examiner thus concluded that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention was made to have made the conjugates of the claimed composition, wherein the conjugates comprise a GM2 ganglioside covalently bound to via lysine residues of KLH, a well-known carrier protein, by reductive amination as taught by Jennings, and to have achieved a ganglioside-KLH molar ratio of between 200:1 to 1400:1, because Neurath teaches that a molar ratio of hapten to carrier protein of 200:1 can be achieved using KLH and using a method that attaches the hapten to KLH via lysine residues.

The Examiner acknowledged that Wiegand fails teach a glycoconjugate within a composition containing a saponin. However, the Examiner stated that Marciani teaches that the use of 20μg of QS-21 as an adjuvant in a genetically-engineered subunit vaccine against feline leukemia virus, and teaches that the choice of QS-21 was important in achieving an immunogenic response to the recombinant viral peptide in that QS-21 was much more effective that alum or oil emulsions in eliciting a humoral response and were protected from viral challenges (citing page 94, col. 2, 2nd full paragraph to page 95, col. 1). The Examiner therefore concluded that it would have been prima facie obvious to one of ordinary skill in the art to have used an adjuvant such as QS-21 because QS-21 appears to be superior to other art known adjuvants such as alum and oil emulsions.

The Examiner stated that although Wiegand teaches a glycoconjugate that comprises a GM2 ganglioside, Wiegand fails to teach a glycoconjugate comprising GD2. However, the Examiner stated that Tsuchida teaches that GD2 is a major ganglioside found in melanoma tumor samples (citing page 48, 2nd col.). The Examiner thus concluded that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used ganglioside other than that of GM2, such as GD2, because Tsuchida teaches that GD2 is a major ganglioside of melanoma cells.

The Examiner also acknowledged that Wiegand fails to teach the specific range of amounts of conjugated ganglioside in a composition, where the amounts are about 1μg to about 200μg. However, the Examiner stated that Livingston teaches immunization of human melanoma patients with a dose of 100μg of an unconjugated GM2 ganglioside preparation (combined with BCG or S. Minnesota mutant R595) that produced an antibody response (citing page 2912, col. 2 to page 2913, and Table 2). The Examiner thus concluded that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have determined the appropriate amounts of KLH-conjugated ganglioside to administer.

The Examiner also stated that the claimed invention is also drawn to methods of treatment, either a method of stimulating or enhancing production of an antibody to GM2 or to GD2, or a method of treating a human subject having

cancer comprising the administration of compositions comprising GM2 or GD2 ganglioside conjugates. The Examiner stated that Wiegand suggests such methods because it teaches that ganglioside conjugates may be used as vaccines. The Examiner also stated that Livingston and Ritter both teach that melanoma patients respond to preparations comprising gangliosides and adjuvants by producing ganglioside and melanoma specific antibodies. The Examiner thus concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention was made to use the ganglioside compositions comprising a conjugate of Wiegand where the carrier protein is KLH, as suggested by Ritter (and also Ratcliff, Patrick and Blincko) and further comprising an adjuvant such as QS-21 as taught by Marciani in methods of treatment for the production of GM2 or GD2 ganglioside antibodies, or for the treatment of a human subject having cancer. Optimization of the dosage, route of immunization, number of sites of immunization to administer the composition is well within the skill of the ordinary artisan.

In response to Examiner's rejection to claims 100, 114, 115 and 117-125, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Briefly, claim 100, as amended, provide a composition which comprises (A) a conjugate of (i) a derivative of a ganglioside, which ganglioside (1) is a GM2 or GD2 ganglioside and (2) comprises an unaltered sphingosine

base, wherein the derivative differs from the ganglioside solely by having an altered sphingosine base which retains only C1 through C4 from the unaltered sphingosine base of the ganglioside, and (ii) Keyhole Limpet Hemocyanin, wherein the GM2 or GD2 ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base and a nitrogen of an ε-aminolysyl group of Keyhole Limpet Hemocyanin; (B) QS-21; and (C) a pharmaceutically acceptable carrier; wherein the amount of the conjugated GM2 or GD2 ganglioside derivative is an amount between about 1 µg and about 200 µg, the amount of QS-21 is an amount of between about 10 µg and about 200 µg, the GM2 or GD2:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, and the relative amounts of such conjugate and QS-21 is effective to stimulate or enhance production in a subject of an antibody to GM2 and GD2, the ganglioside, the derivative of which is present in the conjugate. Claims 114, 115 and 117-125, as amended, provide for methods of stimulating or enhancing production of an antibody to GM2 or GD3 in a subject, and methods of treating a human subject having cancer, e.g., melanoma, by administering said composition to the subject.

The claimed invention is based on applicants' *surprising discovery* that a conjugate of a ganglioside derivative covalently bound to Keyhole Limpet Hemocyanin, e.g., GM2-KLH, with QS-21 as an adjuvant, creates is a strikingly immunogenic vaccine, far superior to previous ganglioside-based vaccines, such as GM2 adherent to the surface of BCG, salmonella Minnesota mutant R595 or

proteosomes, GM2-KLH only, and GM2-KLH plus DETOX or BCG, with regard to (1) higher IgM and IgG antibody titers against GM2 and (2) a decrease in systemic and local adverse reactions related to administrating to a subject. See instant specification, page 58, line 24 to page 59, line 19, and page 93, line 16 to page 95, line 15.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

The references cited against the rejected claims fail to support a *prima facie* case of obviousness. Here, the cited references fail to support a *prima facie* case of obviousness. Specifically, to support a *prima facie* case of obviousness, one of ordinary skill would have to have been motivated to combine the teachings of the cited references at the time of the invention. Moreover, these references would also have to provide a reasonable expectation of success.

It is stressed that the Examiner has based this rejection on the teachings of no fewer than *ten* references. Collectively, these references teach (1) a chemical modification of the sphingosine portion of glycosphingolipids and the subsequent coupling of such modified glycosphingolipids to other molecules, e.g.,

protein, (2) the preparation of antigenic polysaccharide-protein conjugates by directly conjugating a protein with an altered polysaccharide, (3) the use of KLH in synthesizing carbohydrate antigens, small peptide antigens and tricyclic antidepressant drugs, (4) covalent attachment of gangliosides to foreign carrier proteins, (5) a radioactive or enzyme labeled synthetic peptide conjugated to KLH which employs a *synthetic peptide:KLH molar ratio* of 200:1, (6) the use of 20μg of QS-21 as an adjuvant in a vaccine for cats against feline leukemia virus, (7) certain gangliosides, such as GM3, GD3, GM2 and GD2, are expressed in human melanoma specimens, and (8) the preparation of GM2-only, GM2/BCG or GM2/R595 vaccines using 100μg of purified, *unmodified* GM2 ganglioside. From these references, the Examiner draws the untenable conclusion that one of ordinary skill in the art would have been motivated to combine, and would have reasonably expected, this combination to work better than previous ganglioside-based compositions in treating cancer, such as melanoma.

Specifically, Wiegand teaches a chemical modification of the sphingoid portion of glycosphingolipids and the subsequence coupling of such modified glycosphingolipids to other molecules, such as proteins. Wiegand also discloses the preparation and subsequent coupling of reductively aminated ozonolysis products of the GM3, GD3, GM2 and GM1 gangliosides. Wiegand, col. 5, line 24 to col. 16. Wiegand, however, does not teach or suggest any particular species of glycosphingolipid that would perform effectively as a vaccine when linked to other molecules to form an immunoconjugate composition, such as

the claimed invention. Also, Wiegand neither teaches nor suggests that the modification and conjugation of a derivative of a particular ganglioside, such as GM2 or GD2, would produce a composition having superior immunogenic properties relative to a composition obtained with the use of any other gangliosides that are listed in the reference.

Furthermore, as acknowledged by the Examiner herself in the outstanding Office Action, Wiegand fails to explicitly teach (1) the GD2 ganglioside, (2) the bond between the aldehyde group of ozonolyzed and reduced ganglioside and a carrier protein would be via a lysine residue of the carrier protein, (3) a glycoconjugate comprising the specific carrier protein, KLH, (4) a glycoconjugate having a ganglioside to KLH molar ratio of about 200:1 to 1400:1, (5) a glycoconjugate within a composition containing a saponin, such as QS-21, and (6) the specific range of amounts of conjugated ganglioside in a composition, where the amounts are about 1μg to about 200μg.

Jennings teaches the preparation of antigenic polysaccharide-protein conjugates by altering a polysaccharide molecule via controlled oxidation and specifically coupling the altered polysaccharide with a free amino group of a protein via reductive amination. Applicants respectfully disagree with the Examiner's contention that the conjugation procedure taught in Jennings, in combination with Wiegand, provides for the identical coupling procedures recited in the claimed invention. Specifically, applicants note that Jennings

teaches *altering* the polysaccharide and *directly* conjugating the modified polysaccharide with a protein, e.g., tetanus toxoid TT, diphtheria toxoid and other proteins derived from bacteria, bovine serum albumin (BSA), or other proteins containing lysine residues such as a synthetic polylysine. Jennings, Abstract; col. 3, lines 3-54; col. 5, line 17 to col. 6, line 10. The claimed invention radically differs from Jennings in that (1) a ganglioside, e.g., GM2 or GD2 ganglioside, is used to conjugate with the carrier protein KLH, (2) the carbohydrate portion of the ganglioside is *unaltered* throughout the conjugation process, and (3) the conjugation between the ganglioside and the carrier protein KLH does not occurs directly on the unaltered carbohydrate portion of the ganglioside, but rather, on the altered sphingosine portion of the altered ceramide portion of the ganglioside. Moreover, Jennings does not teach nor suggest KLH as a carrier protein. Thus, Jennings actually *teaches away* from the claimed invention by encouraging one skilled in the art to modify carbohydrates and directly conjugate carrier proteins to the terminal portion of the altered carbohydrate, and use carrier proteins other than KLH.

Ratcliff, Patrick and Blincko only teach that the carrier protein KLH may be useful in the synthesis of carbohydrate antigens, small peptides antigens and for tricyclic antidepressant drugs, respectively. None of these references teach or suggest any gangliosides, such as GM2 or GD2 ganglioside, let alone specifically conjugating KLH with any gangliosides. Ratcliff merely provides a general list of carriers suitable for the

synthesis of carbohydrate antigens. Such carriers "include proteins, such as the appropriate serum albumin, such as human or bovine serum albumin, keyhole limpet hemacyanin, tetanus toxoid, and the like." Ratcliff, col. 9, lines 1-4. Ratcliff does not teach or suggest the use of a particular carrier conjugated to a ganglioside that would produce a composition having superior immunogenic properties to treat cancer, such as melanoma.

Patrick discloses a laundry list of suitable carrier proteins for creating small peptides antigens. Patrick, col. 9, lines 7-28. Similar to Ratcliff, Patrick does not teach or suggest the use of a particular carrier, i.e., KLH, conjugated to a ganglioside that would produce a composition having superior immunogenic properties to treat cancer, such as melanoma.

Blincko provides a list of carrier proteins which include "keyhole limpet haemacyanin (KLH), bovine serum albumin (BSA), human serum albumin (HSA), polytufsin or other repeating unit polypeptides, polyamino acids or random copolymers of amino acids, or lysozyme or other enzymes." Blincko, col. 7, lines 29-37. Blincko discloses that KLH as the more preferred carrier protein since immunogens in which the carrier protein which comprises KLH are found particularly effective in raising high titre antisera. Blincko, col. 7, lines 37-42. However, applicants stress that Blincko neither teaches nor suggests a ganglioside or the conjugation of KLH to a ganglioside.

Ritter teaches that the "covalent attachment of

gangliosides to foreign carrier proteins such as KLH" can induce consistent IgG antibodies to gangiosides in the mouse. Ritter, page 406, col. 1. Ritter also teaches KLH-GM2 conjugates. However, Ritter does not describe the chemical nature of the conjugate or of how to make the conjugate. Hence, Ritter neither discloses anything conjugated through the ceramide portion of a ganglioside, nor enables making a conjugate where "the GM2 or GD2 ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphinosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin." Furthermore, Ritter does not teach or suggest (1) an adjuvant such as QS-21, (2) the 200:1 to 1400:1 GM2 or GD2 lactone:KLH molar ratio, or (3) the specified amounts of conjugated GM2 or GD2 ganglioside derivative recited in the rejected claims, as amended.

Neurath discloses a radioactive or enzyme labeled synthetic peptide of no more than 60 amino acids conjugated to KLH, which is employed as a diagnostic tool to determine the presence of Hepatitis B surface antigen. Neurath discloses a *synthetic peptide:KLH* molar ratio of 200:1. Nowhere does Neurath teach or suggest any gangliosides, particularly the GM2 or GD2 ganglioside, glycoconjugates or a ganglioside:KLH molar ratio. Furthermore, Neurath's specific teaching of a synthetic peptide-KLH molar ratio of 200:1 does not teach the range of values, i.e., "from 200:1 to 1400:1" of ganglioside-KLH molar ratios as claimed in the instant invention.

Marciani teaches the use of 20μg of QS-21 as an adjuvant

in a vaccine for cats against feline leukemia virus. Marciani also teaches that the vaccine consists of a recombinant protein, rgp70D, which is a non-glycosylated protein derived from the envelope glycoprotein of FeLV subgroup A envelope gene, that is absorbed on to aluminium hydroxide and used in conjunction with QS-21. Although Marciani teaches that "the purified saponin component elicted a high titre antibody response and also induced an affinity maturation of these antibodies," applicants strongly note that this observation is strictly limited to QS-21 when used in conjunction with a feline leukemia virus vaccine for cats. Nowhere would one skilled in the art associate this reference with the claimed invention. In other words, Marciani does not teach any gangliosides, glycoconjugates or the use of QS-21 with a glycoconjugate. Therefore, Marciani does not provide a motivation to combine such reference in combination with any of the cited references. To consider otherwise would be hindsight.

Tsuchida teaches certain gangliosides, such as GM3, GD3, GM2 and GD2, are expressed in human melanoma specimens. Nowhere in Tsuchida does it suggest cleaving the C4 position of the sphingosine base of any ganglioside to create a ganglioside derivative, and covalently binding such ganglioside derivative to Keyhole Limpet Hemocyanin. Nor does Tsuchida teach using such ganglioside derivative with QS-21 as an adjuvant. Furthermore, Tsuchida does not teach any of the numerical values and ranges recited in the claimed invention.

Livingston discloses vaccines containing either purified

GM2 only or purified GM2 with BCG or R595 as adjuvants. Livingston also discloses the preparation of such GM2 vaccines containing 100μg of purified, *unaltered* GM2 ganglioside. Livingston, page 2912, col. 2. Livingston radically departs from the claimed invention in that it neither teaches an *altered* ganglioside derivative that is *conjugated* to *KLH* nor the use of QS-21 as an adjuvant. Furthermore, the 100μg amount taught in Livingston applies only to unaltered GM2. Without a teaching to suggest otherwise, Livingston fails to teach the limitation of "the amount of the conjugated GM2 or GD2 ganglioside derivative is an amount between about 1μg to 200μg" recited in claims 100, 112, 114 and 115, as amended.

According to the M.P.E.P. §2143.01,

> "[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."

In re Mills, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). As demonstrated above, there is simply no motivation or suggestion to combine the cited references to create the instant invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of the applicants' invention and underlying discovery. None of the references cited by the Examiner give any suggestion, motivation or "indication of which

parameters [are] critical or [a] direction as to which of many possible choices is likely to be successful" to one skilled in the art to create (1) a composition which comprises (A) a conjugate of (i) a derivative of a ganglioside, which ganglioside (1) is a GM2 or GD2 ganglioside and (2) comprises an unaltered sphingosine base, wherein the derivative differs from the ganglioside solely by having an altered sphingosine base which retains only C1 through C4 from the unaltered sphingosine base of the ganglioside, and (ii) Keyhole Limpet Hemocyanin, wherein the GM2 or GD2 ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base and a nitrogen of an ε-aminolysyl group of Keyhole Limpet Hemocyanin; (B) QS-21; and (C) a pharmaceutically acceptable carrier; wherein the amount of the conjugated GM2 or GD2 ganglioside derivative is an amount between about 1 µg and about 200 µg, the amount of QS-21 is an amount of between about 10 µg and about 200 µg, the GM2 or GD2:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, and the relative amounts of such conjugate and QS-21 is effective to stimulate or enhance production in a subject of an antibody to GM2 and GD2, the ganglioside, the derivative of which is present in the conjugate, (2) methods of stimulating or enhancing production of an antibody to GM2 or GD2 in a subject by administering said composition to the subject, or (3) methods of treating a human subject having cancer, e.g., melanoma, by administering said composition to the subject. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Essentially, one skilled in the art would have had to conduct undue experimentation

to achieve applicants' successful yet unexpected result.

Assuming for the sake of argument that the combination of Wiegand, Jennings, Neurath, Ratcliff, Patrick, Blincko, Marciani, Ritter, Tsuchida, and Livingston established a *prima facie* case of obviousness (which applicants vigorously dispute), applicants respectfully maintain that any such *prima facie* rejection would be rebutted by the fact that the claimed invention demonstrates an unexpected advantage, e.g., markedly superior immunogenic results when compared to previous ganglioside-based vaccines, such as GM2/BCG or GM2-KLH plus DETOX or BCG, with regard to (1) higher titers of IgM and IgG antibodies specific for GM2 even at lower doses, and (2) a decrease in systemic and local adverse reactions related to administrating to a subject.

Applicants' specification teaches that QS-21, at *any* of the dosage used, resulted in a *qualitatively different* response than those achieved with the prior art adjuvants to GM2 ganglioside. Instant specification, page 93, line 16 to page 95, line 15. The immunogenic responses achieved with the use of GM2-KLH vaccines alone or with optimal doses of BCG or DETOX were *substantially less effective* than the claimed invention which includes QS-21. For example, even at the 10μg dose, all patients who were treated with the claimed composition produced IgG antibodies detectable by dot blot immune stains against GM2. On the other hand, with the same amount as above, patients who were treated with GM2-KLH alone or with optimal doses of BCG, salmonella Minnesota mutant R595 or proteosomes had only rarely resulted in more than 1

detectable IgG response per 6 immunized patients. Instant specification, page 94, lines 20-27.

The instant specification also teaches that local reactions to dosages of 100-200μg of QS-21 were "quite different" in terms of local adverse reactions than those seen with comparable dosages of BCG and DETOX. Instant specification, page 94, line 5. It states that the local response is more diffuse than the response generally seen with doses of DETOX or BCG inducing comparable systemic symptoms. Instant specification, page 94, lines 8-11. It additionally teaches that a surprising feature of the subjects' response to QS-21 was that several days later (at most 10 days later) the local reactions had completely abated and there was no evidence that the vaccination had been administered to that site. Instant specification, page 97, Table 6. Furthermore, at the 100μg dose, patients treated with the claimed invention showed resulted in only 2 episodes of low grade fever in 44 injections and the local inflammatory responses, which were limited to 2-4 days, did not interfere with daily activities. Instant specification, page 93, lines 29-34.

Therefore, in view of the surprising nature of this invention, one of ordinary skill in the art would *not* have been able to predict, based on the cited references, whether the claimed invention would be *more effectively* immunogenic even at low dosages, and result in a decrease in systemic and local adverse reactions. Moreover, one of ordinary skill certainly would not have reasonably expected the superior effects over to previous ganglioside-based vaccines, such as GM2/BCG or GM2-KLH

plus DETOX or BCG as discussed above. To maintain otherwise would be hindsight.

In view of the above remarks, applicants maintain that claims 100, 114, 115 and 117-125, as amended, satisfy the requirements of 35 U.S.C. §103(a).

The Examiner also rejected claims 115 and 116 under 35 U.S.C. §103(a) as allegedly unpatentable over Wiegand (U.S. Patent No. 5,599,914, issued February 4, 1997) in view of Jennings (U.S. Patent No. 4,356,170, issued October 26, 1982), in view of Neurath (U.S. Patent No. 4,591,552, issued May 27, 1986), in view of Ratcliff (U.S. Patent No. 5,344,870, issued September 6, 1994), in view of Patrick (U.S. Patent No. 4,652,629, issued March 24, 1987), in view of Blincko (U.S. Patent No. 5,256,409, issued October 26, 1993), in view of Marciani (Vaccine, 9:89-96 (February 1991)), in view of Ritter (Seminars in Cancer Biology, 2:401-409 (1991)), in view of Tsuchida (Journal of the National Cancer Institute, 78:45-54 (1987)), in view of Livingston (Proc. Natl. Acad. Sci. USA, 84:2911-2915 (May 1987)), and further in view of Irie (U.S. Patent No. 4,557,931, issued December 10, 1985).

The Examiner stated that claims 115 and 116 also read on methods of treatment of tumors of epithelial origin. The Examiner stated that the combination of Wiegand, Jennings, Neurath, Ratcliff, Patrick, Blincko, Marciani, Ritter, Tsuchida, and Livingston fail to teach treating a cancer of epithelial origin. However, the Examiner stated that Irie teaches that the ganglioside GM2 is

found on or in tumors of a variety of histological types including melanoma and breast carcinoma (citing col. 1, lines 28-31), which is an example of a tumor of epithelial origin. The Examiner thus concluded that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the ganglioside compositions comprising a conjugate of Wiegand where the ganglioside was a GM2, where the carrier protein is KLH, as suggested by Ritter (and also Ratcliff, Patrick and Blincko) and further comprising an adjuvant such as QS-21 as taught by Marciani in methods for the treatment of a human subject having an epithelial cancer.

In response to the Examiner's rejection of claims 115 and 116, applicants respectfully traverse this rejection for the reasons provided below.

Briefly, claims 115 and 116, as amended, provide for methods of treating a human subject having cancer which comprises administering to the subject an effective cancer-treating amount of a composition which comprises (A) a conjugate of (i) a derivative of a ganglioside, which ganglioside (1) is a GM2 or GD2 ganglioside and (2) comprises an unaltered sphingosine base, wherein the derivative differs from the ganglioside solely by having an altered sphingosine base which retains only C1 through C4 from the unaltered sphingosine base of the ganglioside, and (ii) Keyhole Limpet Hemocyanin, wherein the GM2 or GD2 ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base

and a nitrogen of an ε-aminolysyl group of Keyhole Limpet Hemocyanin; (B) QS-21; and (C) a pharmaceutically acceptable carrier; wherein the amount of the conjugated GM2 or GD2 ganglioside derivative is an amount between about 1 µg and about 200 µg, the amount of QS-21 is an amount of between about 10 µg and about 200 µg, the GM2 or GD2:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, and the relative amounts of such conjugate and QS-21 is effective to stimulate or enhance production in a subject of an antibody to GM2 and GD2, the ganglioside, the derivative of which is present in the conjugate. In one embodiment, the cancer is of epithelial origin.

The references cited against claims 115 and 116 also fail to support a *prima facie* case of obviousness.

It is stressed that the Examiner has based this rejection on the teachings of no fewer than *eleven* references. Wiegand, Jennings, Neurath, Ratcliff, Patrick, Blincko, Marciani, Ritter, Tsuchida, and Livingston have been discussed above.

Irie teaches that the GM2 ganglioside is found on or in tumors of a variety of histological types, including melanomas and breast carcinomas. Irie, however, does not provide the elements missing from the references discussed above, i.e., it does not disclose or suggest the claimed composition comprising a conjugate covalently bound as recited in the claims, and also including QS-21, or a method of using such composition to enhance or stimulate antibody production, to treat cancer, or to

prevent relapse of melanoma in patients at risk of such relapse, or the numerical values recited in the claimed invention. For this reason, claims 115 and 116, as amended, are patentably distinct over Irie in combination of Wiegand, Jennings, Neurath, Ratcliff, Patrick, Blincko, Marciani, Ritter and Livingston.

Moreover, as discussed above, the claimed invention demonstrates an unexpected advantage, e.g., markedly superior immunogenic results to previous ganglioside-based vaccines, such as GM2/BCG or GM2-KLH plus DETOX or BCG, with regard to (1) higher titers of IgM and IgG antibodies specific for GM2 even at lower doses, and (2) a decrease in systemic and local adverse reactions related to administrating to a subject.

In view of the above remarks, applicants maintain that claims 115 and 116, as amended, satisfy the requirements of 35 U.S.C. §103(a).

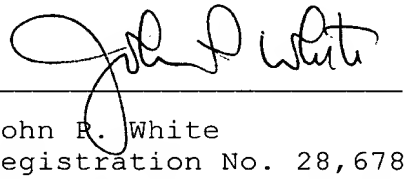
Summary

Applicants maintain that claims 100, 106, 107, 109, 110 and 112-125, as amended, herein are now in condition for allowance. Accordingly, a notice of allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $490.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if an additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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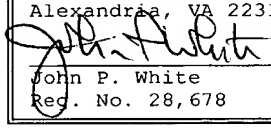

10/18/04

John P. White Date
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Fax Notes:

Proposed examiner's amendment for 08/196,154. Please note that claim 126 needs to be cancelled because it has the same scope as claim 129. Also, because of amendment to 08/477,147, this case needs a T.D. over 08/477,147.

My telephone number is 571-272-0833. Anne Holleran

Date and time of transmission: Tuesday, February 03, 2004 11:33:32 AM
Number of pages including this cover sheet: 08

EXHIBIT A
Applicants: Livingston et al.
U.S. Serial No.: 08/477,097
Filed: June 7, 1995

Application/Control Number: 08/196,154
Art Unit: 1642

PROPOSED EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with xxx on xxx.

The application has been amended as follows:

In the specification:

at page 38, line 13, after "(Kensil et al. 1991)", the following was added:

Coursely chopped Q. saponaria bark [approximately 1 cm square, obtained from Hauser Chemicals, Boulder, CO] was stirred with 10 ml of water/g of bark at room temperature for 1 h. The extract was centrifuged and the supernatant containing the solubilized saponins was saved. The extraction step was repeated on the bark pellet and the two supernatants were pooled. To remove nonsaponin components, the supernatant pool was lyophilized, redissolved in 40 mM acetic acid in water at a concentration of 250 mg/ml (w:v) and either chromatographed through Sephadex G-50 (medium, Pharmacia, Piscataway, NJ) in 40 mM acetic acid with the hemolytic activity localized in the void volume fraction, or dialyzed against 40 mM acetic acid with the hemolytic activity retained by the dialysis membrane. The hemolytic fraction was lyophilized and redissolved at a concentration of 200 mg/ml in 40 mM acetic acid in

chloroform/methanol/water (62/32/6, v/v/v): 1 g of this fraction was applied to Silica Lichroprep (E.M. Science, Gibbston, NJ: 40 to 63 µm particle size, 2.5 cm I.D. x 20 cm height) and eluted isocratically in the solvent used to solubilize the saponins. The elution of saponins was monitored by carbohydrate assay. Fractions containing he saponins of interest were identified by reverse phase TLC with visualization with Bial's reagent (Sigma, ST. Louis, M)) pooled individually, and rotavapped to dryness. The fractions from the silica chromatography were then redissolved in 40 mM acetic acid in 50% methanol and loaded on a semipreparative HPLC column (Vydac C_4, 5µm particle size, 3000 nm pore size, 10 mm I.D. X 25 cm length). Saponin peaks detectd by absorbance at 214 nm were eluted by using a methanol gradient at a flow rate of 4 ml/min and individually rotavapped to dryness. Purity of saponins was assessed by analytic HPLC (Vydac C_4, 5µ particle size, 3000 nm pore size, 4.6 mm I.D. x 25 cm length) with a gradient of 0.1% TFA in acetonitrile. QS-21 is defined as the adjvant active reverse phase HPLC fraction 21 from Q. Saponaria bark extract.

In the claims:

Claim 126 was canceled.

Claim 119. A composition which comprises:

a) a conjugate of (i) a GM2 ganglioside derivative [which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising an altered sphingosine base], wherein the GM2 ganglioside derivative is a GM2 ganglioside cleaved

with ozone, and wherein an aldehyde group is introduced at the C4 position of the sphingosine portion of the GM2 ganglioside, and (ii) Keyhole Limpet Hemocyanin[;], wherein the GM2 ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the sphingosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin;

b) QS-21[, a saponin derivable from the bark of a Quillaja saponaria Molina tree]; and

c) a pharmaceutically acceptable carrier;

wherein the amount of the conjugated GM2 ganglioside derivative is an amount between about 1 μg and about 200 μg, the amount of [the saponin] QS-21 is an amount between about 10 μg and about 200 μg, and the GM2: Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, the relative amounts of such conjugate and [such saponin] QS-21 being effective to stimulate or enhance production in a subject of an antibody to GM2[,]

[wherein in the conjugate the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin].

Claim 127. The composition of 119 wherein the amount of the [saponin] QS-21 is about 200 μg.

Claim 129 The composition of claim 119 which comprises:

a) a conjugate of (i) a GM2 ganglioside derivative [which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising an altered sphingosine base], wherein the GM2 ganglioside derivative is a GM2 ganglioside cleaved with ozone, and wherein an aldehyde group is introduced at the C4 position of the sphingosine portion of the GM2 ganglioside, and (ii) Keyhole Limpet Hemocyanin[;], wherein the GM2 ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the sphingosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin;

b) QS-21[, a saponin derivable from the bark of a Quillaja saponaria Molina tree]; and

c) a pharmaceutically acceptable carrier,

wherein the conjugated GM2 ganglioside derivative is present in an amount between about 1 μg and about 200 μg, the amount of [the saponin] QS-21 is about 100 μg and the GM2: Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, the relative amounts of such conjugate and [such saponin] QS-21 is effective to stimulate or enhance production in a subject of an antibody to GM2[,]

[wherein in the conjugate the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin].

Claim 131. A method of stimulating or enhancing production of an antibody directed to GM2 in a subject which comprises administering to the subject an effective amount of a composition which comprises:

a) a conjugate of (i) a GM2 ganglioside derivative [which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising an altered sphingosine base], wherein the GM2 ganglioside derivative is a GM2 ganglioside cleaved with ozone, and wherein an aldehyde group is introduced at the C4 position of the sphingosine portion of the GM2 ganglioside, and (ii) Keyhole Limpet Hemocyanin[;], wherein the GM2 ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the sphingosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin;

b) QS-21[, a saponin derivable from the bark of a Quillaja saponaria Molina tree]; and

c) a pharmaceutically acceptable carrier;

wherein the amount of the conjugated GM2 ganglioside derivative is present in an amount between about 1 μg and about 200 μg, the amount of [the saponin] QS-21 is amount between about 10 μg and about 200 μg, and the GM2: Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, the relative amounts of such conjugate and [such saponin] QS-21 is effective to stimulate or enhance production in a subject of an antibody to GM2[,]

[wherein in the conjugate the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4

carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin] so as to thereby stimulate or enhance production in said subject of [the antibody] antibodies directed to GM2.

Claim 132. A method of treating a human subject which comprises administering to the subject an effective amount of a composition which comprises:

a) a conjugate of (i) a GM2 ganglioside derivative [which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising an altered sphingosine base], wherein the GM2 ganglioside derivative is a GM2 ganglioside cleaved with ozone, and wherein an aldehyde group is introduced at the C4 position of the sphingosine portion of the GM2 ganglioside, and (ii) Keyhole Limpet Hemocyanin[;], wherein the GM2 ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the sphingosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin;

b) QS-21[, a saponin derivable from the bark of a Quillaja saponaria Molina tree]; and

c) a pharmaceutically acceptable carrier;

wherein the amount of the conjugated GM2 ganglioside derivative is present in an amount between about 1 μg and about 200 μg, the amount of [the saponin] QS-21 is amount between about 10 μg and about 200 μg, and the GM2: Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, the relative amounts of such conjugate

and [such saponin] QS-21 is effective to stimulate or enhance production in a subject of an antibody to GM2[,]

[wherein in the conjugate the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin] so as to stimulate or enhance production in the subject of [the antibody] antibodies to GM2 and thereby treat the subject.

Claim 142. The method of claim 141, wherein the conjugate and the [saponin] QS-21 are mixed on the day of administration to the subject.

TO Farley COMPANY: 2/3/2004 12:03 PM

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Fax Notes:

This is proposed examiner's amendment for 08/481,809. Please note that due to the proposed examiner's amendment of claim 138, claim 139 needs to be canceled because it will have the same scope as claim 138. Claim 145 needs to be canceled because it has the same scope as claim 148.

My telephone number is 571 272 0833. Anne Holleran

Date and time of transmission: Tuesday, February 03, 2004 11:39:04 AM
Number of pages including this cover sheet: 08

EXHIBIT B
Applicants: Livingston et al.
U.S. Serial No.: 08/477,097
Filed: June 7, 1995

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with xxx on xxx.

The application has been amended as follows:

In the specification:

at page 38, line 13, after "(Kensil et al. 1991)", the following was added:

Coursely chopped Q. saponaria bark [approximately 1 cm square, obtained from Hauser Chemicals, Boulder, CO] was stirred with 10 ml of water/g of bark at room temperature for 1 h. The extract was centrifuged and the supernatant containing the solubilized saponins was saved. The extraction step was repeated on the bark pellet and the two supernatants were pooled. To remove nonsaponin components, the supernatant pool was lyophilized, redissolved in 40 mM acetic acid in water at a concentration of 250 mg/ml (w:v) and either chromatographed through Sephadex G-50 (medium, Pharmacia, Piscataway, NJ) in 40 mM acetic acid with the hemolytic activity localized in the void volume fraction, or dialyzed against 40 mM acetic acid with the hemolytic activity retained by the dialysis membrane. The hemolytic fraction was lyophilized and redissolved at a concentration of 200 mg/ml in 40 mM acetic acid in

chloroform/methanol/water (62/32/6, v/v/v): 1 g of this fraction was applied to Silica Lichroprep (E.M. Science, Gibbston, NJ: 40 to 63 µm particle size, 2.5 cm I.D. x 20 cm height) and eluted isocratically in the solvent used to solubilize the saponins. The elution of saponins was monitored by carbohydrate assay. Fractions containing he saponins of interest were identified by reverse phase TLC with visualization with Bial's reagent (Sigma, ST. Louis, M)) pooled individually, and rotavapped to dryness. The fractions from the silica chromatography were then redissolved in 40 mM acetic acid in 50% methanol and loaded on a semipreparative HPLC column (Vydac C_4, 5µm particle size, 3000 nm pore size, 10 mm I.D. X 25 cm length). Saponin peaks detectd by absorbance at 214 nm were eluted by using a methanol gradient at a flow rate of 4 ml/min and individually rotavapped to dryness. Purity of saponins was assessed by analytic HPLC (Vydac C_4, 5µ particle size, 3000 nm pore size, 4.6 mm I.D. x 25 cm length) with a gradient of 0.1% TFA in acetonitrile. QS-21 is defined as the adjvant active reverse phase HPLC fraction 21 from Q. Saponaria bark extract.

In the claims:

Claims 139 and 145 were canceled.

Claim 138. A composition which comprises:

a) a conjugate of (i) a ganglioside derivative [an oligosaccharide portion of a ganglioside comprising an altered ceramide moiety including an altered sphingosine base], wherein the ganglioside derivative is a ganglioside cleaved with ozone, and wherein an aldehyde group is introduced at the C4 position of the sphingosine portion

of the ganglioside, and (ii) Keyhole Limpet Hemocyanin[an immunogenic protein-based carrier;], wherein the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the sphingosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin;

b) QS-21[, a saponin derivable from the bark of a Quillaja saponaria Molina tree]; and

c) a pharmaceutically acceptable carrier;

wherein the amount of the conjugated [oligosaccharide portion of the]ganglioside derivative is an amount between about 1 μg and about 200 μg, the amount of [the saponin] QS-21 is an amount between about 10 μg and about 200 μg, and [when the ganglioside is GM2 the GM2:Keyhole Limpet Hemocyanin] the ganglioside:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, the relative amounts of such conjugate and [such saponin] QS-21 being effective to stimulate or enhance production in a subject of an antibody to the ganglioside,

[wherein in the conjugate the oligosaccharide portion of the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin through a C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative and to an ε-aminolysyl group of Keyhole Limpet Hemocyanin, wherein the C-4 carbon is present in a CH_2 group].

Claim 146. The composition of 138 wherein the amount of the [saponin] QS-21 is about 200 μg.

Claim 148 The composition of claim 138 which comprises:

a) a conjugate of (i) ganglioside derivative [an oligosaccharide portion of a ganglioside comprising an altered ceramide moiety including an altered sphingosine base], wherein the ganglioside derivative is a ganglioside cleaved with ozone, and wherein an aldehyde group is introduced at the C4 position of the sphingosine portion of the ganglioside, and (ii) Keyhole Limpet Hemocyanin[an immunogenic protein-based carrier;], wherein the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the sphingosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin;

b) QS-21[, a saponin derivable from the bark of a Quillaja saponaria Molina tree]; and

c) a pharmaceutically acceptable carrier,

wherein the amount of the conjugated [oligosaccharide portion of the]ganglioside derivative is an amount between about 1 μg and about 200 μg, the amount of [the saponin] QS-21 is about 100 μg, and [when the ganglioside is GM2 the GM2:Keyhole Limpet Hemocyanin] the ganglioside:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, the relative amounts of such conjugate and [such saponin] QS-21 being effective to stimulate or enhance production in a subject of an antibody to the ganglioside,

[wherein in the conjugate the oligosaccharide portion of the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin through a C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside]

derivative and to an ε-aminolysyl group of Keyhole Limpet Hemocyanin, wherein the C-4 carbon is present in a CH_2 group and].

Claim 150. A method of stimulating or enhancing production of antibodies to a ganglioside in a subject which comprises administering to the subject an effective amount of a composition which comprises:

a) a conjugate of (i) a ganglioside derivative [an oligosaccharide portion of a ganglioside comprising an altered ceramide moiety including an altered sphingosine base], wherein the ganglioside derivative is a ganglioside cleaved with ozone, and wherein an aldehyde group is introduced at the C4 position of the sphingosine portion of the ganglioside, and (ii) Keyhole Limpet Hemocyanin[an immunogenic protein-based carrier;], wherein the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the sphingosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin;

b) QS-21[, a saponin derivable from the bark of a Quillaja saponaria Molina tree]; and

c) a pharmaceutically acceptable carrier;

wherein the amount of the conjugated [oligosaccharide portion of the]ganglioside derivative is an amount between about 1 μg and about 200 μg, the amount of [the saponin] QS-21 is an amount between about 10 μg and about 200 μg, and [when the ganglioside is GM2 the GM2:Keyhole Limpet Hemocyanin] the ganglioside:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, the relative amounts of such conjugate and

[such saponin] QS-21 being effective to stimulate or enhance production in a subject of an antibody to the ganglioside,

[wherein in the conjugate the oligosaccharide portion of the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin through a C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative and to an ε-aminolysyl group of Keyhole Limpet Hemocyanin, wherein the C-4 carbon is present in a CH_2 group, and] so as to thereby stimulate or enhance production in the subject of the antibody to the ganglioside.

Claim 151. A method of treating a human subject having cancer which comprises administering to the subject an effective amount of a composition which comprises:

a) a conjugate of (i) a ganglioside derivative [an oligosaccharide portion of a ganglioside comprising an altered ceramide moiety including an altered sphingosine base], wherein the ganglioside derivative is a ganglioside cleaved with ozone, and wherein an aldehyde group is introduced at the C4 position of the sphingosine portion of the ganglioside, and (ii) Keyhole Limpet Hemocyanin[an immunogenic protein-based carrier;], wherein the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the sphingosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin;

b) QS-21[, a saponin derivable from the bark of a Quillaja saponaria Molina tree]; and

c) a pharmaceutically acceptable carrier;

wherein the amount of the conjugated [oligosaccharide portion of the]ganglioside derivative is an amount between about 1 μg and about 200 μg, the amount of [the saponin] QS-21 is an amount between about 10 μg and about 200 μg, and [when the ganglioside is GM2 the GM2:Keyhole Limpet Hemocyanin] the ganglioside:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, the relative amounts of such conjugate and [such saponin] QS-21 being effective to stimulate or enhance production in a subject of an antibody to the ganglioside,

[wherein in the conjugate the oligosaccharide portion of the ganglioside derivative is covalently bound to the Keyhole Limpet Hemocyanin through a C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative and to an ε-aminolysyl group of Keyhole Limpet Hemocyanin, wherein the C-4 carbon is present in a CH_2 group, and] so as to thereby stimulate or enhance production in the subject of the antibody to the ganglioside.

Claim 161. The method of claim 160, wherein the conjugate and the [saponin] QS-21 are mixed on the day of administration to the subject.

Interview Summary	Application No.	Applicant(s)	
	08/196,154	LIVINGSTON ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

All participants (applicant, applicant's representative, PTO personnel):

1) *Anne Holleran*. (3)_____.

2) *Mark Farley*. (4)_____.

Date of Interview: *on or about 2/6/04*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Discussed proposed Examiner's amendment that was faxed on 2/3/2004. Mr. Farley indicated that he would look over proposed examiner's amendment and show it to applicant and get back to the examiner*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

_____
Examiner's signature, if required

EXHIBIT C
Applicants: Livingston et al.
U.S. Serial No.: 08/477,097
Filed: June 7, 1995

Summary of Record of Interview Requirements

ıual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

ɔmplete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the lication whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews

Paragraph (b)

very instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as ranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and demark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself ɔmplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless ɛ examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies ıich bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the erview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction quirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing t typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the bstance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the ontents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the nclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address ıer with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other ɔumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It ɔould be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview nless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the ubstance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and ccurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the tatement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the aper recording the substance of the interview along with the date and the examiner's initials.

Interview Summary	Application No.	Applicant(s)	
	08/481,809	LIVINGSTON ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Anne Holleran*. (3)_____.

(2) *Mark Farley*. (4)_____.

Date of Interview: *on or about 2/6/04*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Discussed proposed Examiner's amendment that was faxed on 2/3/2004. Mr. Farley indicated that he would look over proposed examiner's amendment and show it to applicant and get back to the examiner*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

_____
Examiner's signature, if required

EXHIBIT D
Applicants: Livingston et al.
U.S. Serial No.: 08/477,097
Filed: June 7, 1995

Summary of Record of Interview Requirements

ıual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

ɔmplete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the lication whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews

Paragraph (b)

very instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as ranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

ɔusiness with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and demark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to ' alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself ɔmplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless ɜ examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies ıich bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the erview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction quirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing ıt typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the ıbstance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the ɔntents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the ınclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address ther with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other rcumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It hould be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview ınless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the ubstance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

47016-A-PCT-US JPW

Interview Summary	Application No.	Applicant(s)
	08/196,154	LIVINGSTON ET AL.
	Examiner	Art Unit
	Anne Holleran	1642

All participants (applicant, applicant's representative, PTO personnel):

(1) *Anne Holleran*. (3) *Cindy Yang*.

(2) *John White*. (4)_____.

Date of Interview: *12 August 2004*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: *119*.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Examiner discussed copy of proposed amendment to the claims and to the specification with applicants' representative. When amendment is filed examiner will discuss 103 rejection with a Biotech Practice Specialist or a Quality Assurance Specialist.*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Anne L. Holleran

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the Interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the Interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

NOTICE OF OFFICE PLAN TO CEASE SUPPLYING COPIES OF CITED U.S. PATENT REFERENCES WITH OFFICE ACTIONS; AND PILOT TO EVALUATE THE ALTERNATIVE OF PROVIDING ELECTRONIC ACCESS TO SUCH U.S. PATENT REFERENCES

Summary

The United States Patent and Trademark Office (Office or USPTO) plans in the near future to: (1) cease mailing copies of U.S. patents and U.S. patent application publications (US patent references) with Office actions except for citations made during the international stage of an international application under the Patent Cooperation Treaty and those made during reexamination proceedings; and (2) provide electronic access to, with convenient downloading capability of, the US patent references cited in an Office action via the Office's private Patent Application Information Retrieval (PAIR) system which has a new feature called "E-Patent Reference." Before ceasing to provide copies of U.S. patent references with Office actions, the Office shall test the feasibility of the E-Patent Reference feature by conducting a two-month pilot project starting with Office actions mailed after December 1, 2003. The Office shall evaluate the pilot project and publish the results in a notice which will be posted on the Office's web site (www.USPTO.gov) and in the Patent Official Gazette (O.G.). In order to use the new E-Patent Reference feature during the pilot period, or when the Office ceases to send copies of U.S. patent references with Office actions, the applicant must: (1) obtain a digital certificate from the Office; (2) obtain a customer number from the Office, and (3) properly associate applications with the customer number. The pilot project does not involve or affect the current Office practice of supplying paper copies of foreign patent documents and non-patent literature with Office actions. Paper copies of references will continue to be provided by the USPTO for searches and written opinions prepared by the USPTO for international applications during the international stage and for reexamination proceedings.

Description of Pilot Project to Provide Electronic Access to Cited U.S. Patent References

On December 1, 2003, the Office will make available a new feature, E-Patent Reference, in the Office's private PAIR system, to allow more convenient downloading of U.S. patents and U.S. patent application publications. The new feature will allow an authorized user of private PAIR to download some or all of the U.S. patents and U.S. patent application publications cited by an examiner on form PTO-892 in Office actions, as well as U.S. patents and U.S. patent application publications submitted by applicants on form PTO/SB08 (1449) as part of an IDS. The retrieval of some or all of the documents may be performed in one downloading step with the documents encoded as Adobe Portable Document format (.pdf) files, which is an improvement over the current page-by-page retrieval capability from other USPTO systems.

Steps to Use the New E-Patent Reference Feature During the Pilot Project and Thereafter

Access to private PAIR is required to utilize E-Patent Reference. If you don't already have access to private PAIR, the Office urges practitioners, and applicants not represented by a practitioner, to take advantage of the transition period to obtain a no-cost USPTO Public Key Infrastructure (PKI) digital certificate, obtain a USPTO customer number, associate all of their pending and new application filings with their customer number, install no-cost software (supplied by the Office) required to access private PAIR and E-Patent Reference feature, and make appropriate arrangements for Internet access. The full instructions for obtaining a PKI digital certificate are available at the Office's Electronic Business Center (EBC) web page at: <http://www.uspto.gov/ebc/downloads.html>. Note that a notarized signature will be required to obtain a digital certificate.

To get a Customer Number, download and complete the Customer Number Request form, PTO-SB125, at: http://www.uspto.gov/web/forms/sb0125.pdf. The completed form can then be transmitted by facsimile to the Electronic Business Center at (703) 308-2840, or mailed to the address on the form. If you are a registered attorney or patent agent, then your registration number must be associated with your customer number. This is accomplished by adding your registration number to the Customer Number Request form. A description of associating a customer number with an application is described at the EBC web page at: http://www.uspto.gov/ebc/registration_pair.html.

The E-Patent Reference feature will be accessed using a new button on the private PAIR screen. Ordinarily all of the cited U.S. patent and U.S. patent application publication references will be available over the Internet using the Office's new E-Patent Reference feature. The size of the references to be downloaded will be displayed by E-Patent Reference so the download time can be estimated. Applicants and registered practitioners can select to download all of the references or any combination of cited references. Selected references will be downloaded as complete documents as Adobe Portable Document Format (.pdf) files. For a limited period of time, the USPTO will include a copy of this notice with Office actions to encourage applicants to use this new feature and, if needed, to take the steps outlined above in order to be able to utilize this new feature during the pilot and thereafter.

During the two-month pilot, the Office will evaluate the stability and capacity of the E-Patent Reference feature to reliably provide electronic access to cited U.S. patent and U.S. patent application publication references. While copies of U.S. patent and U.S. patent application publication references cited by examiners will continue to be mailed with Office actions during the pilot project, applicants are encouraged to use the private PAIR and the E-Patent Reference feature to electronically access and download cited U.S. patent and U.S. patent application publication references so the Office will be able to objectively evaluate its performance. The public is encouraged to submit comments to the Office on the usability and performance of the E-Patent Reference feature during the pilot. Further, during the pilot period registered practitioners, and applicants not represented by a practitioner, are encouraged to experiment with the feature, develop a proficiency in using the feature, and establish new internal processes for using the new access to the cited U.S. patents and U.S. patent application publications to prepare for the anticipated cessation of the current Office practice of supplying copies of such cited

references. The Office plans to continue to provide access to the E-Patent Reference feature during its evaluation of the pilot.

Comments

Comments concerning the E-Patent Reference feature should be in writing and directed to the Electronic Business Center (EBC) at the USPTO by electronic mail at eReference@uspto.gov or by facsimile to (703) 308-2840. Comments will be posted and made available for public inspection. To ensure that comments are considered in the evaluation of the pilot project, comments should be submitted in writing by January 15, 2004.

Comments with respect to specific applications should be sent to the Technology Centers' customer service centers. Comments concerning digital certificates, customer numbers, and associating customer numbers with applications should be sent to the Electronic Business Center (EBC) at the USPTO by facsimile at (703) 308-2840 or by e-mail at EBC@uspto.gov.

Implementation after Pilot

After the pilot, its evaluation, and publication of a subsequent notice as indicated above, the Office expects to implement its plan to cease mailing paper copies of U.S. patent references cited during examination of non provisional applications on or after February 2, 2004; although copies of cited foreign patent documents, as well as non-patent literature, will still be mailed to the applicant until such time as substantially all applications have been scanned into IFW.

For Further Information Contact

Technical information on the operation of the IFW system can be found on the USPTO website at http://www.uspto.gov/web/patents/ifw/index.html. Comments concerning the E-Patent Reference feature and questions concerning the operation of the PAIR system should be directed to the EBC at the USPTO at (866) 217-9197. The EBC may also be contacted by facsimile at (703) 308-2840 or by e-mail at EBC@uspto.gov.

Date. 12/1/03

Nicholas P. Godici

Nicholas P. Godici
Commissioner for Patents

USPTO TO PROVIDE ELECTRONIC ACCESS TO CITED U.S. PATENT REFERENCES WITH OFFICE ACTIONS AND CEASE SUPPLYING PAPER COPIES

In support of its 21st Century Strategic Plan goal of increased patent e-Government, beginning in June 2004, the United States Patent and Trademark Office (Office or USPTO) will begin the phase-in of its E-Patent Reference program and hence will: (1) **provide downloading capability of the U.S. patents and U.S. patent application publications cited in Office actions** via the E-Patent Reference feature of the Office's Patent Application Information Retrieval (PAIR) system; and (2) **cease mailing paper copies of U.S. patents and U.S. patent application publications with Office actions** (in applications and during reexamination proceedings) except for citations made during the international stage of an international application under the Patent Cooperation Treaty (PCT). In order to use the new E-Patent Reference feature applicants must: (1) obtain a digital certificate and software from the Office; (2) obtain a customer number from the Office; and (3) properly associate patent applications with the customer number. Alternatively, copies of all U.S. patents and patent application publications can be accessed without a digital certificate from the USPTO web site, from the USPTO Office of Public Records, and from commercial sources. The Office will continue the practice of supplying paper copies of foreign patent documents and non-patent literature with Office actions. Paper copies of cited references will continue to be provided by the USPTO for international applications during the international stage.

Schedule

June 2004	TCs 1600, 1700, 2800 and 2900
July 2004	TCs 3600 and 3700
August 2004	TCs 2100 and 2600

All U.S. patents and U.S. patent application publications are available on the USPTO web site. However, a simple system for downloading the cited U.S. patents and patent application publications has been established for applicants, called the E-Patent Reference system. As E-Patent Reference and Private PAIR require participating applicants to have a customer number, retrieval software and a digital certificate, all applicants are strongly encouraged to contact the Patent Electronic Business Center to acquire these items. To be ready to use this system by June 1, 2004, contact the Patent EBC as soon as possible by phone at 866-217-9197 (toll-free), 703-305-3028 or 703-308-6845 or electronically via the Internet at ebc@uspto.gov.

Other Options

The E-Patent Reference function requires the applicant to use the secure Private PAIR system, which establishes confidential communications with the applicant. Applicants using this facility must receive a digital certificate, as described above. Other options for obtaining patents which do not require the digital certificate include the USPTO's free Patents on the Web program (http://www.uspto.gov/patft/index.html). The USPTO's Office of Public Records also supplies copies of patents for a fee (http://ebiz1.uspto.gov/oems25p/index.html). Commercial sources also provide U.S. patents and patent application publications.

For complete instructions see the Official Gazette Notice, USPTO TO PROVIDE ELECTRONIC ACCESS TO CITED U.S. PATENT REFERENCES WITH OFFICE ACTIONS AND CEASE SUPPLYING PAPER COPIES, on the USPTO web site.

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Please find below and/or attached an Office communication concerning this application or proceeding.